

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)

PATENT

REMARKS

Claims 12 and 27-29 are pending in the present application. Claim 27 has been amended herein. No new matter has been added. Upon entry of the present amendment, claims 12 and 27-29 will remain pending. **Because the amendment to the claims removes an issue for appeal (i.e., indefiniteness), Applicants respectfully request that they be entered into the record. See, M.P.E.P. §714.12. No further search or consideration is necessary.**

I. The Claimed Invention Is Not Obvious

Claims 12 and 27-29 are rejected under 35 U.S.C. §103(a) as allegedly being obvious over Walters et al., Drug Discovery Today, 1998, 3(4), 160-178 (hereinafter, the "Walters reference"). The Office Action asserts that the Walters reference teaches "presenting components of the virtual library as combination of reagents and corresponding reactions" and evaluating "members of the library by their synthesizability," and, thus, it would have been "obvious to one skilled in the art to characterized any compound of interest, and thus to extend, if needed, such characterization to each compound of the library." (See, Office Action dated December 30, 2003). Applicants traverse the rejection and respectfully request reconsideration thereof.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on Applicant's disclosure. *In re Vaeck*, 20 U.S.P.Q.2d 1438 (Fed. Cir. 1991). Significantly, the Walters reference does not teach or suggest all the features recited in Applicants' claims.

Claim 12 recites, in part, that the compounds of the virtual library are dissected into their constituent fragments and subsequently tracking the virtual synthetic addition of these fragments. The Walters reference does not teach or suggest dissecting the compounds of a virtual library into their constituent fragments, where the constituent fragment is associated with at least

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)**PATENT**

one reagent that represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments, let alone track the virtual synthetic addition. Rather, the Walters reference reviews the state of the art in virtual screening and reports the many problems associated therewith. In particular, the Walters reference primarily deals with the construction and screening of virtual libraries.

The only portion of the Walters reference actually referred to in the present Office Action is Figure 1 on page 161 (no portion of the Walters reference was actually referred to in the previous Office Action dated December 30, 2003). The Office Action asserts that Figure 1 is seen as "representation of member of a compound library dissected into fragments and presented as a synthetic round leading to the target compound." Figure 1 of the Walters reference, however, is described as followed by the authors of the Walters reference at page 160:

There are perhaps millions of chemical 'libraries' that a trained chemist could reasonably hope to synthesize. Each library can, in principle, contain a huge number of compounds – easily billions. Combinatorial chemists have already demonstrated, in several prototype systems, that libraries containing 1,000-100,000 compounds can in fact be assembled. Figures 1-3 give simple examples that have appeared in the literature recently. In Figure 1, 1,4-benzodiazepine scaffold is shown, along with the components from which this scaffold might be assembled. In the same fashion, Figure 2 shows a pyrrolidine library and Figure 3 shows an acylpiperidine library. The 'building blocks' are in many cases very simple and can readily be purchased or synthesized. In each of these three examples, it can easily be imagined that the library could contain 10^9 or more possible compounds. A reasonable conclusion from the preceding analysis is that a 'virtual chemistry space' exists that contains perhaps 10^{100} possible molecules (Box 1). (citations omitted)

Thus, quite clearly, the authors are referring to Figure 1 to provide an example of "building blocks" (i.e, components) from which a scaffold could be assembled. Thus, this portion of the Walters reference amounts to nothing more than a combinatorial method for building a scaffold from "building blocks." Nowhere does this portion of the Walters reference teach or suggest dissecting compounds (as opposed to building scaffolds from "building blocks") into constituent fragments, where the constituent fragment is associated with at least one reagent that represents a

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)**PATENT**

necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments.

The Office Action dated December 30, 2003 refers to a "chemically aware builder" that is alleged to comprise "presenting components of the virtual library as combination of reagents and corresponding reactions" and further asserts that the compounds generated thereby are "defined by synthetic rounds between its chemical components" (see, page 3 of the Office Action). The only portion of the Walters reference that refers to a "chemically aware builder" that Applicants are able to locate is Figure 13 on page 169. The Walters reference refers to Figure 13 on page 168 as follows:

Working in the forward direction – limiting the compounds constructed – seems to be the more straightforward approach to implement and provides a natural fit with current thinking about the assembly of real combinatorial libraries. Construction of a library on the computer uses a set of 'allowed' building blocks and reactions, such as is given in Figure 13. A limit can be placed on the number of building blocks that are allowed in any molecule – for example, no more than four building blocks assembled from three reactions. The library of building blocks can also be limited to those that are either commercially available or readily and cheaply synthesized. Ideally, such molecule-building programs should apply detailed knowledge of cross-reactivity (i.e., functional groups that are not compatible) to help eliminate molecules that could not be readily synthesized in practice. These programs, such as CONJURE are capable of processing hundreds of thousands of compounds per hour on a single workstation.

Thus, the "chemically aware builder" that the Walters reference refers to is one which limits the kinds of compounds that are constructed by limiting the number and type of building blocks and reactions used. This portion of the Walters reference fails to teach or suggest that the virtual synthetic addition of constituent fragments of the compounds according to the synthetic method for the compound is tracked in any manner. Indeed, Applicants' specification teaches tracking the virtual synthetic addition of the constituent fragments (i.e., accounting for the fragments being introduced, the related transformations or reactions associated with the fragments, and the alternate transformations that lead to the introduction of a common fragment into the desired compounds) at, for example, page 14, line 23 to page 15, line 8, and page 17, line 27 to page 28, line 7 of the specification.

- 5 -

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)

PATENT

The Office Action dated December 30, 2003 also refers to "Computer-Aided Estimation of Synthetic Accessibility" stating that such software "evaluates members of the library by their synthesizability." The only portion of the Walters reference that refers to a "Computer-Aided Estimation of Synthetic Accessibility" that Applicants are able to locate is on page 169. The Walters reference refers to "Computer-Aided Estimation of Synthetic Accessibility" on page 169 as follows:

Johnson and coworkers have adopted the CAOS [computer-aided organic synthesis] paradigm into the high-throughput world with a program called CAESA (Computer-Aided Estimation of Synthetic Accessibility) that is designed to rank the synthesizability of a series of candidate molecules generated by a *de novo* design program. CAESA uses a library of generalized synthetic transformations in conjunction with an analysis of features such as stereocenters to determine which molecules can be easily synthesized.

Again, this portion of the Walters reference fails to teach or suggest that the virtual synthetic addition of constituent fragments of the compounds according to the synthetic method for the compound is tracked in any manner.

Thus, the prior art reference (the Walters reference) does not teach or suggest all the features recited in the claims. Although the Walters reference reports an overview of virtual screening of compounds, and also reports the existence of computer software for carrying out particular functions, the Walters reference fails to teach or suggest a method of identifying *in silico* each compound of a virtual library of compounds wherein the compounds are dissected into constituent fragments, where the constituent fragment is associated with at least one reagent that represents a necessary chemical to introduce the constituent fragment into the compound, and where the dissecting is based on the ease of synthesis of the compound from the constituent fragments, adding the constituent fragments together in sequential synthesis rounds defining thereby a synthetic method for the compound from the constituent fragments, and tracking the virtual synthetic addition of constituent fragments of the compounds. Thus, the claimed invention is not obvious in view of the Walters reference. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. §103(a) be withdrawn.

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)**PATENT****II. Obviousness-Type Double Patenting**

Claim 12 is rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 8 and 9 of U.S. Patent No. 6,253,168 (hereinafter, the "168 patent"). Applicants traverse this rejection and respectfully request reconsideration because the claimed subject matter is not an obvious variant.

An obviousness-type double patenting rejection is analogous to a failure to meet the nonobviousness requirement of 35 U.S.C. §103. *In re Braithwaite*, 154 U.S.P.Q. 29, 34 (C.C.P.A. 1967) and *In re Longi*, 225 U.S.P.Q. 645, 648 n.4 (Fed. Cir. 1985). Thus, under the law, the pivotal question in an obviousness-type double patenting analysis is: Does any claim in the application define merely an obvious variation of an invention disclosed and claimed in the patent? *In re Vogel*, 164 U.S.P.Q. 619 (C.C.P.A. 1970). If the answer to this question is no, there can be no double patenting. In making this analysis, then, the proper inquiry is as taught in *Graham v. John Deere Co.*, 383 U.S. 1 (1966). See, M.P.E.P. §804. No such analysis is even attempted in the Office Action.

For the record, claims 8 and 9 of the '168 patents read as follows:

8. A method of generating a database comprising information about the member compounds of a virtual library of compounds comprising:

- selecting each of said compounds for said virtual library
- and, for each, dissecting each of said compounds into fragments;
- linking together the fragments of each of the compounds;
- tracking the sequence of linkage for each compound;
- grouping two or more compounds of said library together to form a mixture;
- grouping a further two or more compounds of said library together to form a further mixture;
- linking together the tracked information of each of the members of said mixture;
- linking together the tracked information of each of the members of said further mixture; and
- storing said tracked information thereby generating a database.

9. A method of generating a database comprising information

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)

PATENT

about member compounds in a virtual library of compounds comprising:
 selecting each of said compounds for said virtual library
and, for each, dissecting said compounds into fragments;
 representing each of said fragments as a transformation
wherein each transformation is a one to one link between a
fragment and a reagent used to introduce said fragment into one of
said compounds;
 linking together the transformations of each of the
compounds;
 tracking the sequence of linkage for each compound; and
 storing said transformation information thereby generating
a database.

The only remarks of record by the Examiner are 1) "generating the database information as claimed in '168 will, therefore, obviously describe (identify) the member compound; further, the methods steps of the instant and referenced claims are the same" (see, page 5 of the Office Action dated December 30, 2003); and 2) "it would be obvious to an artisan that information obtained by generating the database information as claimed in the reference will serve as a descriptor and identifier of a target compound" (see, page 6 of the present Office Action).

Clearly this limited "analysis" is not sufficient under *Graham v. John Deere Co.* In addition, the methods steps recited in claim 12 of the present application and the method steps of claims 8 and 9 of the '168 patent are clearly not the same. Further, as stated previously, the Examiner in the present application has restricted "Claims 12, 13, drawn to method of identifying compounds" from "Claims 14-26, drawn to method of storing information" (see, Restriction requirement dated May 20, 2002). Clearly, methods of "generating a database comprising information about the member compounds of a virtual library of compounds" (see preamble of claim 8 of the '168 patent) and "generating a database comprising information about member compounds in a virtual library of compounds" (see preamble of claim 9 of the '168 patent) are, indeed, methods of "storing information." That the "groups" in the present application are not identical to the recited claims in the '168 patent are not "identical" completely misses the point. Thus, the Office Action fails to establish a *prima facie* case of obviousness-type double patenting in view of the foregoing comments. Accordingly, Applicants respectfully request that this rejection be withdrawn.

DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)**PATENT****III. The Claimed Invention Is Supported by Ample Written Description**

Claim 29 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Office Action asserts that recitation of "formation of constituent fragments for which the reverse transformation is known" lacks support in the specification. Applicants traverse the rejection and respectfully request reconsideration because the specification provides ample written description supporting the claimed inventions.

At page 4, line 31 t page 5, line 4, Applicants recite:

Thus a variety of components of fragments may be identified, each of which lend themselves to readily available reagents or reactions to generate diverse compounds. Further, each fragment is associated with at least one reagent, which represents the necessary chemical to be used to introduce that desired fragment into the compound being generated *in silico*.

Thus, if each of the fragments lend themselves to readily available reagents, and if each fragment is associated with at least one reagent that represents the necessary chemical to be used to introduce that desired fragment into the compound being generated *in silico*, then the "reverse transformation" of the formation of the constituent fragments (i.e., synthesis of the compound from the constituent fragments) is known. Further, the entire specification teaches and provides examples of dissecting a compound into constituent fragments whereby the constituent fragments are known to be used as "building blocks" for the compound (i.e., reverse transformation) in the first place.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. §112, first paragraph, as allegedly failing to provide sufficient written description be withdrawn.

IV. The Claims Are Clear And Definite

Claim 27 is rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as their invention. The Office Action asserts that because base claim 12 recites


DOCKET NO.: IBIS0036-101 (IBIS-0005US.C1)**PATENT**

that dissecting the compound into fragments is based on the ease of synthesis, recitation of "the dissecting is based on commercial availability of constituent fragments" is indefinite. Although Applicants disagree, solely to advance prosecution of the present application, Applicants have amended claim 27 to recite that dissecting is based further on the commercial availability of reagents. Support for the amendment can be found at, for example, page 5, lines 4-5 of the specification.

V. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6914 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,


Paul K. Legaard, Ph.D.
Registration No. 38,534

Date: 25 August 2004

COZEN O'CONNOR
1900 Market Street
Philadelphia, PA 19103-3508
Telephone: (215) 665-6914
Facsimile: (215) 701-2141